UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JAN 3 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review Meeting on **BIFENTHRIN 3rd**

FROM: Esther Rinde, Ph.D. E.R.
Manager, Carcinogenicity Peer Review
Health Effects Division (H7509c)

TO: Addressees

Attached for your review is a package on **Bifenthrin** prepared by **Dr. Byron Backus.** Bifenthrin was previously classified by the Carcinogenicity Peer Review Committee and by SAP (Documents are attached).

A meeting to re-consider the carcinogenicity classification of **Bifnthrin** is scheduled for **Wednesday Jan. 22, 1992,** at **10:00 am in Room 821, CM2.**

Addressees

P. Fenner-Crisp
W. Burnam
R. Engler
R. Hill
R. Beliles
K. Baetcke
L. Brennecke
M. Van Gemert
M. Copley
K. Dearfield
J. Parker
H. Pettigrew
W. Sette
G. Ghali
B. Fisher
J. Du
Y. Woo
J. Quest
E. Saito (for microfiche-with one-liner)
A. Clevenger
E. Andersen
B. Backus
C. Swentzel

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Bifenthrin (FMC 54800): Request for Re-evaluation of its Carcinogenic Classification

TO: Esther Rinde, Ph.D.
Manager, Peer Review Committee for Carcinogenicity
SACB/HED (H7509C)

FROM: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 1/2/92
Toxicology Branch 2
HED (H7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 1/2/92
Section Head, Review Section 2
Toxicology Branch 2
HED (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 1/2/92
Toxicology Branch 2
HED (H7509C)

Background

Bifenthrin is currently classified as a category C carcinogen, with a Q_1* of 5.4×10^{-2} $(mg/kg/day)^{-1}$. The primary basis of this classification is a mouse carcinogenicity study (report issued February 3, 1986) in which it was originally reported that incidences of leiomyosarcoma of the urinary bladder of male mice were 2/48, 6/50, 8/50, 7/50, and 14/49 at 0, 50, 200, 500, and 600 ppm (the Q_1* was calculated from these urinary bladder leiomyosarcoma findings).

In addition to the urinary bladder findings in male mice, the same study also showed a significant dose-related trend (but no significant pairwise trends) for liver tumors in males (combined incidences of hepatocellular adenomas and adenocarcinomas: 2/41, 2/43, 4/43, 4/39, and 7/40 for 0, 50, 200, 500, and 600 ppm respectively). There was no significant dose-related trend for lung tumors in females, but the 50, 200, and 600 ppm dose groups had significantly higher incidences than the controls (14/49, 26/47, 23/47, 19/47, 23/45 for 0, 50, 200, 500, and 600 ppm respectively).

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Bifenthrin was reviewed by the Peer Review Committee on April 10, 1987. In the subsequent Peer Review memorandum (June 2, 1987) Bifenthrin was classified as a category C carcinogen on the basis of "the uncommon nature of the urinary bladder tumors seen in the Swiss-Webster mice and because of the limited but supportive evidence derived from the incidence of both lung and liver neoplasms seen in the same study." In a memorandum dated March 16, 1988, the Scientific Advisory Panel agreed with the category C classification for Bifenthrin, "based on the significant occurrence only at the high dose of leiomyosarcoma in urinary bladders of male mice." However, the Panel did not believe that quantitative risk assessment was warranted, "based upon the lack of any dose response data in any animal model and the inappropriateness in applying mathematical models to data that do not show a dose response." In a second peer review, it was stated (memorandum dated June 9, 1988) that: "the Committee was divided on whether a quantification of risk should be performed but favored quantification because of the uncommon nature of the tumor type."

The registrant, FMC, has now submitted additional information on the mouse carcinogenicity to the Agency relating to identification of the male urinary bladder tumors as leiomyosarcomas (Dr. Will Butler, the pathologist who has re-reviewed the slides, has stated that these are more aptly described as hemangiopericytomas, and that "lesions" may be a better term than "tumors"). In addition, five more of these "tumors" (or lesions) have been reported for the control males.

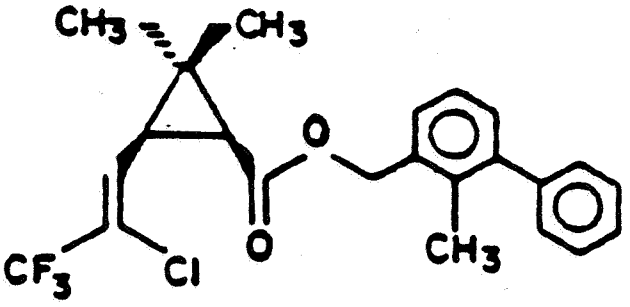
This reviewer requests that the Peer Review Committee evaluate the additional information submitted by FMC, along with other relevant data to determine whether there is sufficient evidence for revising the carcinogenic classification of Bifenthrin.

A. Information on Bifenthrin

Bifenthrin (sometimes spelled Biphenthrin), also known as FMC 54800,[chemical name: 2-methyl[1,1'-biphenyl]-3-yl)methyl-cis, trans-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropanecarboxylate] is a synthetic pyrethroid, used as both an insecticide and acaracide. Current registered uses include application to ornamentals and some food crops. Current tolerances (permanent and temporary) include 0.5 ppm on cottonseed, 0.1 ppm in meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep, and 0.02 ppm in milk. A number of Section 18 emergency exemptions have been issued.

The Caswell (or Tox Chem) Number of Bifenthrin is 463F. The Chemical Abstracts Registry Number (CAS No.) is 82657-04-3.

--- Structure of Bifenthrin ---



[2-Methyl-(1,1'biphenyl)-3-yl]-methyl-cis, trans-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropanecarboxylate

B. Evaluation of Carcinogenicity Evidence:

1. Swiss-Webster Mouse Carcinogenicity Study

Reference: Geiger, L.E., Barbera, J., and Ballester, E.J. "Oncogenicity Study of FMC 54800: Lifetime Feeding Study in Albino Mice." February 3, 1986. Acc. nos. 261948, 261949, 261950, 261951, 261952, 261953, 261954, and 261955. Lab Study No. A83-974. Testing Facility: FMC Toxicology Laboratory, Somerville, NJ.

Reference: Butler, W.H. "Oncogenicity Lifetime Feeding Study in Albino Mice: Histopathological Review of Selected Sections of Liver, Lung and Urinary Bladder." Revised report date: June 3, 1991. In MRID 419016-01. Lab Study No. A83-974.

Reference: Butler, W.H., Cohen, S.M., and Squire, R.A. "Review of Selected Sections of Bladder from FMC Study A83-974: A 2 Year Study on FMC 54800 in the Swiss-Webster Mouse." In MRID 419016-01.

Reference: Butler, W.H. "Oncogenicity Lifetime Feeding Study in Albino Mice: Histopathological Review of Selected Sections of Liver, Lung and Urinary Bladder: Addendum." Report date: November 13, 1991. In MRID 420993-01. (This document was submitted in response to a meeting held at EPA on August 21, 1991. The text of this reference is appended to this memorandum).

a. Experimental Design

FMC 54800 technical (88.35%, with an isomer ratio of 98% cis and 2% trans) was administered in the diet to groups of 50 male and 50 female Swiss-Webster Tac(SW)fBR mice at 0 (control), 50, 200, 500, or 600 ppm for 87 weeks (males) and 92 weeks (females).

b. Discussion of Tumor Data

Since the last peer review on bifenthrin, all slides prepared from the urinary bladders of the male mice in the mouse carcinogenicity study on this chemical have been reevaluated by W. H. Butler. Those slides in which tumors (or lesions) were observed by Dr. Butler were also evaluated by Dr. S. M. Cohen and Dr. R. A. Squire.

Regarding the classification of these bladder tumors, the three pathologists agree that these tumors (or lesions) are not leiomyosarcomas (as originally reported) or even leiomyomas (both types would have originated from smooth muscle tissue). The following is taken directly from the report by Butler, Cohen and Squire:

"The main consistent histological features of the tumors are the presence of abnormal vascular spaces, smooth muscle, large epitheloid cells and an inflammatory infiltrate. Where it is possible to identify the anatomical region of bladder the tumors are located in the trigone region and are often associated with small arteries... While it is not possible to accurately define the histogenesis of this lesion, the origin appeared to be from the vascular mesenchyme of the trigonal arteries."

From p. 10 of the addendum of November 13, 1991, by Dr. Butler: "The panel of three pathologists concluded that the mouse bladder tumor observed in the bifenthrin study was not a leiomyosarcoma but rather that the tumor arose in the submucosa and may arise from the vascular mesenchyme. At the August meeting with EPA, I stated that the most apt term for this type lesion is hemangiopericytoma." The addendum also includes a photomicrograph of a PTAH-stained leiomyosarcoma from a rat (the entire field is made up of purple-stained muscle fibers) compared with a PTAH-stained lesion from a 600 ppm mouse (no indication of purple-stained muscle fibers).

In a letter dated December 31, 1991 (see the appended copy) to Dr. Morelli of FMC, Dr. S. M. Cohen stated that he agreed with Dr. Butler that the most appropriate name for these lesions is hemangiopericytoma, noting also that these lesions have no counterpart in the human bladder.

As originally reported, the incidences of "leiomyosarcoma" of the urinary bladder in male mice were 2/48, 6/50, 8/50, 7/50, and 14/49 at 0, 50, 200, 500, and 600 ppm, respectively. While incidences of this tumor were elevated in all male groups exposed to Bifenthrin (and the P value associated with positive trend was 0.00053) only the incidence at 600 ppm was significantly ($p < 0.01$) different from that of controls.

The following incidences of leiomyosarcomas of the urinary bladder were calculated (memorandum of April 8, 1987, from Richard Levy to Byron Backus) from the original report:

Dose ppm	0	50	200	500	600
	2/46 (4)	6/48 (12)	8/48 (17)	7/45 (16)	14/45 (31)**

However, on further examination of urinary bladders from the male mice, Dr. Butler observed "five additional bladder lesions in control mice" and Drs. S.M. Cohen and R.A. Squire

concurred with this finding. Based on this, the following "urinary bladder tumor rates" have been calculated:

Dose ppm	0	50	200	500	600
	7/47 (15)	6/48 (12)	8/48 (17)	7/45 (16)	14/45 (31)

With these incidences, the P value associated with positive trend becomes 0.025; largely because of the increased incidence for these tumors (or lesions) in the 600 ppm group. However, the incidence at 500 ppm is essentially the same as that for the controls.

Questions relating to historical control data for the bladder lesions, the increased incidence of larger ("macroscopic") urinary bladder lesions in 600 ppm males, and differentiation between the adenomas and hyperplasias diagnosed in the liver, are addressed by Dr. Butler in the document titled: "Oncogenicity Lifetime Feeding Study in Albino Mice: Histopathological Review of Selected Sections of Liver, Lung and Urinary Bladder: Addendum." A copy of the text is appended to this memorandum. It is noted that Butler states (with respect to the only other long-term mouse study conducted at FMC) "that six lesions of the lamina propria were observed in the bladders of male control mice. These lesions are histologically the same as those seen in the bifenthrin study." This incidence is slightly higher than that previously reported (according to the June 2, 1987 Peer Review memorandum: "Historical control data on Swiss Webster mice were available from only one other study... The incidence of leiomyosarcomas of the urinary bladder in this study was 4/49 in males and 0/49 in females.").

c. Non-neoplastic Lesions

There were slight increases in incidences of glandular hyperplasias of the stomach (not significant by Fisher's Exact Test) and retinal atrophy (significant by Fisher's Exact Test) in males and females of the highest (600 ppm) dose group. The males of this group also showed an increased incidence of cortical atrophy of the adrenal gland. Incidences of bilateral germinal epithelial degeneration of the testes were significantly elevated in males of groups 2, 3, 5 (incidences of 4/49, 8/32, 8/26, 8/38, and 12/49 for 0, 50, 200, 500, and 600 ppm respectively).

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Dietary exposure levels were selected on the basis of results from two 28-day studies. In the first, no effects were noted at 0, 50, 100, 200, or 300 ppm. In the second, the concentrations were 0, 500, 600, 750, and 1000 ppm. At 1000 ppm all female mice died by day 12 and 7/10 males by day 7. At 750 ppm 5/10 females died by day 6 (with clonic convulsions) but there were no mortalities among males.

Tremors were observed in all males and females of the 500 and 600 ppm exposure groups during the first 3 months of the study.

2. Sprague-Dawley Rat Carcinogenicity Study

Reference: McCarty, J.D., Barbera, J., Ballester, E.J., and Geiger, L.E. "Oncogenicity Study of FMC 54800: 2 Year (734 Day) Feeding Study in Albino Rats." January 31, 1986. Acc. nos. 261940, 261941, 261942, 261943, 261944, 261945, 261946, and 261947. Lab Study No. A83-952. Testing Facility: FMC Toxicology Laboratory, Somerville, NJ.

a. Experimental Design

FMC 54800 technical (88.35%, with an isomer ratio of 98% cis and 2% trans) was administered in the diet for 734 days to groups of 50 male and 50 female Sprague-Dawley rats at 0 (control), 12, 50, 100, and 200 ppm.

b. Discussion of Tumor Data

For the most common tumors (pituitary adenoma, adrenal cortical adenoma, adrenal medullary neoplasm - benign and malignant) there were no indications of a dose-relationship. Incidences of pancreatic cell adenoma in males were 1/47, 0/25, 0/27, 0/31, and 3/50 for the 0, 12, 50, 100, and 200 ppm groups respectively. Incidences of fibrosarcoma in males were 0/50, 1/50, 0/50, 0/50, 3/50 for the 0, 12, 50, 100, and 200 ppm groups respectively.

In the peer review memorandum dated June 2, 1987, it is stated: "The Committee did not feel that the occurrence of either tumor type was compound related, i.e. statistical significance was not achieved for either tumor type neither in trend analysis nor in pairwise comparison and for pancreatic islet tumors, historical control data indicates that this is not a particularly rare tumor type in this strain of rat."

c. Non-neoplastic Lesions

Pituitary congestion was observed in 3/36 females at 200 ppm (vs. 0/44 controls), and was not observed in females at any other dose level. Nonglandular gastritis was observed in 3/48 males and 2/49 females at 200 ppm (controls: 1/40 and 0/49), while retinal degeneration was observed in 3/28 females at 200 ppm (0/42 controls).

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Dose levels were selected on the basis of a 28-day range-finding study in which all rats at 400 ppm died by day 15, and 6/10 males and 1/10 females at 300 ppm died by day 20.

In this study, tremors were observed in all 200 ppm males in the period from day 4 to day 28, and in all 200 ppm females in the period from day 4 to day 30.

C. Additional Toxicology Data on Bifenthrin

1. Reference Dose

The reference dose (RfD) is 0.015 mg/kg body weight/day, based on a NOEL of 1.5 mg/kg bwt/day and an uncertainty factor of 100. The NOEL value was derived from a one year dog feeding study in which tremors resulted and has been approved by both the HED (11/6/87) and Agency (7/20/88) reference dose committees.

2. Metabolism

In oral dosing studies using C14-labeled bifenthrin, most (about 70%) of the radioactivity was recovered in the feces, and was found to be due to the parent compound and its hydroxylated metabolites. Some (20%) radioactivity was excreted in the urine; compounds present were hydrolytic and hydrolytic/oxidative degradation products of the parent compound. The major metabolic route in plasma appears to be hydrolysis of the ester linkage with oxidation of the resulting alcohol to the acid. Significant bioaccumulation of the parent compound can occur in tissues (including skin) with high fat content, with half-lives in these tissues of about 50 days.

3. Mutagenicity

a. Salmonella (Ames) assay: In an acceptable study, Bifenthrin technical was negative both with and without S9 activation in strains TA98, TA100, TA1535, TA1537, and TA1538. In addition, FMC has submitted acceptable Ames studies - all with negative findings - for three impurities (FMC 102032, FMC 78162, FMC 78161) present in technical Bifenthrin.

b. Chromosomal aberrations in CHO cells: In an acceptable study, Bifenthrin (FMC 54800) doses ranging from 100 to 10000 µg/ml with and without S9 activation did not cause an increased incidence of chromosomal aberrations in CHO cells.

c. Chromosomal aberrations in rat bone marrow cells: In an acceptable study, Bifenthrin, administered orally to rats at 3, 10, or 30 mg/kg/day over a 5 day period, did not cause an increase in severity or incidence of chromosomal aberrations in bone marrow cells.

d. HGPRT locus mutation in mouse lymphoma cells: In an acceptable study, bifenthrin was tested at 15.8, 50, 158, and 500 µg/ml (1st assay) and 50, 150, and 200 µg/ml (second assay) with and without concurrent exposure to rat S9. Solubility limit of the test material was 200 µg/ml. Under the assay conditions there was no indication that the test material elicited a mutagenic response.

e. Forward mutation at the TK locus in mouse lymphoma cells: In an acceptable study, doses of 0.042 to 0.24 µl/ml without S9 resulted in a 1.8 to 4.2x dose-dependent increase in mutation frequency at the TK locus. Doses of 0.024 to 0.1 µl/ml caused a 1.3 to 2.0x dose-dependent increase in mutation frequency. The test material was considered to be mutagenic both with and without S9 in this assay.

f. Unscheduled DNA synthesis in rat hepatocytes: Two studies have been submitted. In the first study, bifenthrin was considered to be mutagenic at 2 µl/ml as there was an average net grain count of 9.3/nucleus as compared with 2.5-3.8 for different controls. There was no indication of any increases in average mean net nuclear grain counts at lower dosage levels (0.1 to 1.0 µl/ml), but the standard deviations associated with these counts were unacceptably high. In the second assay, there was no evidence of UDS at doses ranging from 1.0 to 2.5 µl/ml using several criteria (increase in average net nuclear grains/nucleus, number of nuclei/exposure level with 5 and/or 20 or more net nuclear grains) for evaluation.

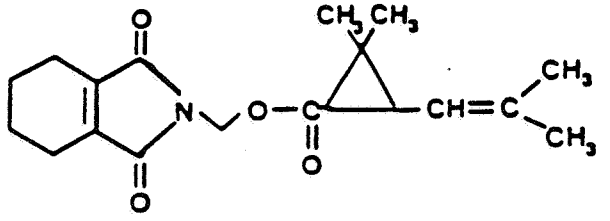
4. Developmental Toxicity

In a study in which bifenthrin was administered by gavage to female rats at 0, 0.5, 1.0 and 2.0 mg/kg/day, the maternal and fetal NOELs were 1.0 mg/kg/day; the maternal LEL was 2 mg/kg/day (tremors occurred); this was also considered the fetal LEL, as there was an increased incidence of hydroureter without hydronephrosis.

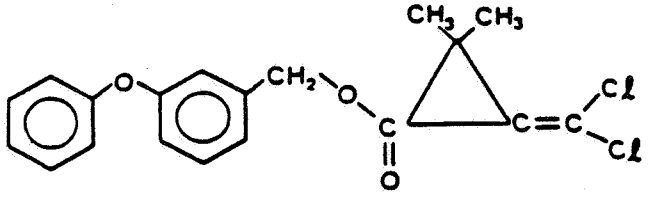
In a rabbit developmental toxicity study, doses administered by gavage were 0, 2.67, 4 and 8 mg/kg/day. The maternal LEL was 4 mg/kg/day (head and forelimb twitching); at 8 mg/kg/day almost all dams showed twitching and tremors, and two aborted, one after having had clonic convulsions. No developmental toxicity was observed at 8 mg/kg/day (HDT).

5. Structure-Activity Correlations

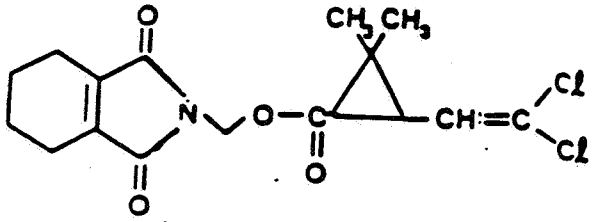
Bifenthrin has some structural similarities to tetramethrin, permethrin, and cypermethrin, which have the following structures:



Tetramethrin



Permethrin



Cypermethrin

Tetramethrin is currently classified as a category C carcinogen without risk assessment quantitation (memorandum of December 11, 1989) on the basis of a statistically significant dose-related increase in the incidence of interstitial cell adenomas in the testes of rats at dietary exposure levels of 1000 ppm and above ppm) dietary exposure levels.

Permethrin is currently classified as a category C carcinogen with a risk assessment quantitation (memorandum of September 18, 1989). The quantitative risk assessment was based on data from a CD-1 mouse study involving a dose-related increase in combined lung adenomas and/or carcinomas observed in females.

Cypermethrin is classified as a "weak" category C carcinogen (memorandum dated February 17, 1988), based on the finding of statistically significant positive dose-related trends for lung adenomas/carcinomas combined and for lung adenomas alone in female SPF mice (101 week study; dietary exposure levels 0, 100, 400 and 1600 ppm). From the memorandum of February 17, 1988: "The evidence (common tumor, one species, one sex, no increase in the proportion of malignant tumors or decrease in the time to tumor occurrence, and lack of mutagenic activity) was not considered strong enough to warrant a quantitative estimation of human risk."

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Bifenthrin

Page _____ is not included in this copy.

Pages _13_ through _25_ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

__X__ FIFRA registration data.

_____ The document is a duplicate of page(s) _____

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

University of Nebraska Medical Center

Department of Pathology and Microbiology
600 South 42nd Street
Omaha, NE 68198-3135
(402) 559-6388
FAX: (402) 559-8018

Samuel M. Cohen, M.D., Ph.D.
Professor and Vice Chairman

December 31, 1991

Dr. Micheal Morelli
FMC Agricultural Chemical Div.
1735 Market St.
Philadelphia, PA 19103

Dear Dr. Morelli:

I have just spoken again with Dr. William Butler regarding the unusual mesenchymal bladder lesions in mice from FMC Project A-83-974. Apparently there is some concern by individuals at the U.S. Environmental Protection Agency to put a specific name on these lesions. After discussions with Dr. Butler, the most reasonable name to give these is hemangiopericytoma, since that is the type of lesion that most closely resembles those that we are observing in the mouse bladder. The more accurate terminology is the longer name which we had given them, that is, a mesenchymal tumor with smooth muscle and pericytomatous differentiation.

It must be kept in mind, however, that although the name hemangiopericytoma is appropriate for the lesions we are seeing in the mouse bladder, these are not the same lesions that are seen as hemangiopericytomas in humans in other tissues, and they have not been reported in the human bladder. A few months ago, I spoke with Dr. Leopold Koss concerning the presence of these lesions in another mouse study in which he was acting as a consultant. As you aware, Dr. Koss is an authority on human bladder pathology, having written the Armed Forces Institute of Pathology fasicle on the the subject. He indicated in our discussions that these unusual lesions in the mouse bladder most he believed were like an hemangiopericytoma, but that they were clearly different from the usual hemangiopericytoma seen in any tissue in humans, and that these lesions have never been seen in the human bladder.

In summary, I therefore agree with Dr. Butler that the most appropriate single name for these mouse bladder lesions is hemangiopericytoma, and also, that these lesions have no counterpart in the human bladder. If I can be of any further assistance with this matter, please do not hesitate to contact me.

Sincerely,

Samuel M. Cohen, M.D., Ph.D.

SMC:gp

xc: William H. Butler, MB, BS, FRCPath

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Bifenthrin, Qualitative Risk Assessment -
Swiss-Webster Mouse Dietary Study

Caswell no.463F

From: Bernice Fisher, Biostatistician Bernice Fisher 12/20/9
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

To: Byron T. Backus, Ph.D., Toxicologist
Review Section II
Herbicide/Fungicide/Antimicrobial Support Branch
Health Effects Division (H7509C)

Thru: Kerry L. Dearfield, Ph.D., Acting Section Head
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C) G. Gahale
12/20/91

Summary

The qualitative risk assessment of bifenthrin was based upon a study of toxicity/oncogenicity in Swiss-Webster mice. The males were fed 0, 50, 200, 500 and 600 ppm of bifenthrin for 87 weeks and the females for 92 weeks. Each dose group included 50 animals of each sex.

A statistical evaluation of mortality indicated no significant incremental changes with dose increments of bifenthrin in either male or female mice.

Male mice had a significant dose related increasing trend in hepatocellular carcinomas and in the combined hepatocellular adenomas and/or carcinomas. They also had a significant dose related increasing trend in urinary bladder submucosal tumor rates.

Female mice had significant differences in the pair-wise comparison of controls and the 50 ppm group in lung adenomas and in the combined lung adenomas and /or carcinomas. They also had a significant difference in the pair-wise comparison of controls and the 200 ppm group in combined lung adenomas and/or carcinomas.

Background

A chronic toxicity/oncogenicity study in Swiss-Webster mice, both sexes, was conducted by FMC Laboratory and issued in February, 1986 (FMC Tox Lab Study no. A83-974).

The study design allocated groups of 50 males/females to dose levels of 0, 50, 200, 500 and 600 ppm of bifenthrin.

This current qualitative risk assessment replaces the previous one(Bifenthrin, Mouse Study - Qualitative and Quantitative Risk Assessment of Combined Toxicity and Oncogenicity Study in Mice, R.Levy et al-April,1987). Survival analysis was not changed while the tumor data and their rates were modified because the Registrant provided new information.

Survival Analysis

In both sexes of mice, there was no statistical evidence of increasing mortality with incremental doses of bifenthrin (Tables 1 and 2).

The statistical evaluation of mortality in the mouse study was based upon the Thomas, Breslow and Gart computer program.

Tumor Analysis

Male mice had a significant increasing trend in hepatocellular combined adenomas and/or carcinomas, hepatocellular carcinomas (Table 3) and in urinary bladder/submucosal tumor rates (Table 4).

Female mice had a statistically significant difference in the pair-wise comparison of controls and the 50 ppm level, in combined lung adenomas and/or carcinomas and in lung adenomas (Table 5). The females also had a significant difference in the pair-wise comparison of controls and the 200 ppm level in combined lung adenomas and/or carcinomas (Table 5).

The above statistical analysis of tumor rates was based upon the Cochran-Armitage Trend test and Fisher's Exact test for pairwise comparisons of controls and each dose group since there was no statistical evidence of incremental mortality with increasing doses of bifenthrin.

Table 1. Bifenthrin - Swiss-Webster Mouse Study, Male Mortality Rates+ and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53-78	79-87[a]	Total
0	1/50	5/49	20/44	10/24	36/50(72)
50	1/50	4/49	17/45	9/28	31/50(62)
200	1/50	5/49	10/44	10/34	26/50(52)
500	4[b]/50	5/46	17/41	9/24	35/48(73)
600	3/50	3/47	10/44	15/34	31/50(62)

+ Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Final sacrifice at week 87.

[b] 2 accidental deaths occurred, one at 6 weeks and one at 14 weeks.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 2. Bifenthrin - Swiss-Webster Mouse Study, Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose(ppm)	1-26	27-52	53-78	79-92[a]	Total
0	2/50	8/48	10/40	11/30	31/50(62)
50	5/50	3/45	13/42	16/29	37/50(74)
200	4/50	3/46	16/43	12/27	35/50(70)
500	3/50	4/47	15/43	7/28	29/50(58)
600	4/50	5/46	9/41	14/32	32/50(64)

[+] Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Final sacrifice at week 92.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 3. Bifenthrin - Swiss-Webster Male Mice, Hepatocellular Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	50	200	500	600
Tumors					
Adenomas	1/43	1/46	0/45	2/40	3[a]/43
(%)	(2)	(2)	(0)	(5)	(7)
p=	0.050	0.735	0.489	0.473	0.308
Carcinomas	0/43	0/46	1/45	2[b]/40	2/43
(%)	(0)	(0)	(2)	(5)	(5)
p=	0.019*	1.000	0.511	0.229	0.247
Both	1/43	1/46	1/45	4/40	5/43
(%)	(2)	(2)	(2)	(10)	(12)
p=	0.004**	0.736	0.741	0.158	0.101

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.

[a] First adenoma observed at week 56, dose 600 ppm.
[b] First carcinoma observed at week 72, dose 500.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 4. Bifenthrin - Swiss-Webster Male Mice, Urinary Bladder Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	50	200	500	600
Tumors					
Submucosal	7/47	6[a]/48	8/48	7/45	14/45
(%)	(15)	(12)	(17)	(16)	(31)
p=	0.025*	0.484	0.518	0.579	0.054

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a] First tumor observed at week 39, dose 50 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 5. Bifenthrin - Swiss-Webster Female Mice, Lung Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	50	200	500	600
Tumors					
Adenomas	12/49	22[a]/47	19/47	15/47	19/45
(%)	(24)	(47)	(40)	(32)	(42)
p=	0.337	0.019*	0.073	0.280	0.054
Carcinomas	2/49	4/47	4[b]/47	4/47	2/45
(%)	(4)	(9)	(9)	(9)	(4)
p=	0.459	0.319	0.319	0.319	0.659
Both	14/49	26/47	23/47	19/47	21/45
(%)	(29)	(55)	(49)	(40)	(47)
p=	0.348	0.007**	0.033*	0.157	0.055

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a] First adenoma observed at week 22, dose 50 ppm.
[b] First carcinoma observed at week 54, dose 200.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

References

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Cochran, W.G. (1954) Some Methods for Strengthening the Comon X^2 Test, Biometrics 10, 417-451.

Cox, D.R. (1972) Regression Models and Life Tables (with discussion) J. Royal Stat. Soc. Ser. B. 34, 187-220.

Thomas, D.G., Breslow, N., and Gart, J.J. (1977) Trend and Homogeneity Analysis of Proportions and Life Life Table Data, Computers and Biomedical Research 10, 373-381.

6/2/87

(35)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 2 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Peer Review of Bifenthrin

From: Judith W. Hauswirth, Ph.D. Judith W Hauswirth 4/28/87
Acting Section Head, Section VI
Toxicology Branch/HED (TS-769C)

To: George La Rocca
Product Manger No. 15
Registration Division (TS-767C)

The Toxicology Branch Peer Review Committee met on April 10, 1987 to discuss and evaluate the weight of the evidence on Bifenthrin, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

Reto Engler — Reto Engler

John A. Quest — John A. Quest

Esther Rinde — Esther Rinde

Louis Kasza — Louis Kasza

Judith W. Hauswirth — Judith W. Hauswirth

Robert Beliles — Robert B Beliles

Donald Barnes — Donald G Barnes

Richard Levy — Richard A. Levy

2. Reviewers: (non-panel members responsible for data presentation signatures indicate technical accuracy of panel report).

Byron T. Backus (Reviewer) — Byron T. Backus

Marcia van Gemert (Section Head) — Marcia van Gemert

C. J. Nelson (Reviewer) cjnelson

Edwin Budd (Section Head) Edwin Budd

3. Peer Review Members in Absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Theodore M. Farber Theodore M. Farber

Anne Barton Anne Barton

William Burnam

Diane Beal Diane Beal

B. Material Reviewed:

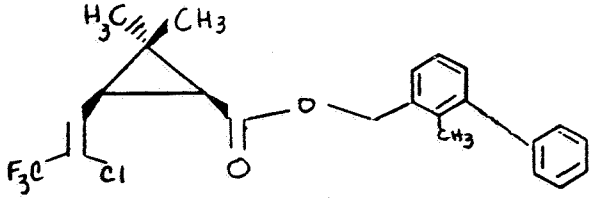
The material available for review consisted of DER's on rat and mouse Bifenthrin oncogenicity studies. company response to Toxicology Branch reviews of the rat and mouse oncogenicity studies, a paper from the open literature by Gammon and Sandar (Neurotoxicology 6(2):63-86, 1985), historical control data, Toxicology Branch "One-Liners" on Bifenthrin and part of a report entitled "Permethrin: Assessment of Chronic and Oncogenic Effects. A Summary", dated September 3, 1982.

C. Background Information:

Bifenthrin (cyclopropanecarboxylic acid, 3-(2-chloro-3,3,3-trifluro-1-propenyl)-2,2-dimethyl-(2-methyl[1,1'-biphenyl]-3-yl)methylester) is a synthetic pyrethroid. Current registrations allow application to ornamentals and other non-food crops. Temporary tolerances have been issued for apples, cottonseed, meat, fat and meat by-products of goats, sheep, cattle, horses and hogs and milk.

Bifenthrin is also referred to as FMC 54800 in this report.

Structure:



D. Evaluation of Oncogenicity Studies:

1. Mouse Oncogenicity Study:

Oncogenicity Study of FMC 54800: Lifetime feeding study in albino mice. Geiger, L. E., Barbera, J. and Ballister, E. Study No. A83-974, conducted at the FMC Toxicology Laboratory. February 3, 1986. Accession Nos. 262948-261955.

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a. Discussion of Study:

FMC 54800 (88.35% pure, with an isomer ratio of 98% cis and 2% trans) was administered in the diet to groups of 50 male and 50 female Swiss-Webster Tac(SW)fBR mice at levels of 0, 50, 200, 500 and 600 ppm. Male mice were fed the diets for a total of 87 weeks and females 92 weeks.

The incidence of relevant tumors seen in this study can be found in the following table.

'Tumor Rates+ of Mice Fed Bifenthrin

Tumor Type	Dose (ppm) 0	50	200	500	600
Males					
Urinary Bladder leiomyosarcoma	2/46(4)**	6/48(12)	8/48(17)	7/45(16)	14/45(31)**
Liver					
adenocarcinoma	0/24*(0)	0/28(0)	1/35(3)	2/24(8)	2/34(6)
adenoma	2/41(5)	2/43(5)	3/43(7)	2/39(5)	5/40(12)
adenoma & adenocarcinoma	2/41*(5)	2/43(5)	4/43(9)	4/39(10)	7/40(18)
Females					
Lung Bronchioal-veolar adenomas & adenocarcinoma	14/49(29)	26/47**(55)	23/47*(49)	19/47(40)	23/45*(51)

The number in parentheses is the percentage incidence.
+Tumor Bearing Animals/Animals at Risk. The number of animals that died prior to the occurrence of the first tumor for each type of tumor are removed from animals at risk.
Note - Significance of trend Analysis (Cochran-Armitage Trend Test) denoted at Control: significance of pairwise comparision with control (Fisher's Exact Test) denoted at Dose level.
* $p<0.05$ ** $p<0.01$

o On the bladder tumors:

Most of the urinary bladder leiomyosarcomas were detected microscopically. However, in at least four males these tumors were macroscopically evident, one at 500 ppm and three at 600 ppm. Although some females were reported to have urinary bladder leiomyosarcomas, there was no dose-response relationship (Control 0/50; 50 ppm, 2/50; 200 ppm, 4/50; 500 ppm, 1/50; 600 ppm 0/49).

Historical control data on Swiss Webster mice were available from only one other study. Females were on test in this study for 93 weeks and males for 98 weeks. The incidence of leiomyosarcomas of the urinary bladder in this study was 4/49 in males and 0/49 in females.

o On the liver tumors:

Liver tumors were found in only male mice with the exception of one hepatocellular adenocarcinoma in a 500 ppm female. No predisposing hepatic changes were observed in the livers of treated animals.

Historical control data were available from only one other study as stated for the urinary bladder tumors above. The incidence of hepatocellular tumors in that study was 1/49 in males. No other historical control data on liver neoplasms were presented for review.

o On the bronchioalveolar tumors (females):

Most of the reported lung tumors were adenocarcinomas. Adenomas were seen in 0 in controls, 1 at 50 ppm, 0 at 200 ppm, 3 at 500 ppm and 1 at 600 ppm.

Historical control data were provided from the conducting laboratory on only one study in which the incidence of combined bronchioalveolar adenomas and adenocarcinomas in female mice was 18/50.

Additional data were available on female Swiss-Webster mice from the open literature and are summarized below (lung tumors only).

Report	Strain Designation and Source	Study Duration	Incidence
Prejean, et al.[1]	SPF Swiss-Webster derived Manor Farms, Staatsburg, NY	540 days	21/153(13.7%)
Buening, et al.[2]	Swiss-Webster BLU:Ha(ICR) Spruce Farms, NY	62-66 wks.	12/21(57%)
Buening, et al.[2]	Swiss-Webster BLU:Ha(ICR) Spruce Farms, NY	62-66 wks.	12/30(50%)
Sher[3]	CFW Carworth Farms	18 mos.	4/100(4%)
Sher[3]	CFW Carworth Farms	18 mos.	10/203(4.9%)
Sher[3]	CFW Carworth Farms	80 wks.	19/60(31.7%)
Sher[3]	Swiss-Webster Carworth Farms	2 yrs.	28/100[a,b]

Sher[3]	Swiss-Webster Carworth Farms	2 yrs.	26/101[a,c]
Sher[3]	Swiss-Webster	18 mos.	1/46(2.2%)
Sher[3]	Swiss-Webster	18 mos.	3/34(8.8%)

a - sex not specified
b - carcinomas only
c - presumably carcinomas only

Although it is difficult to compare the above data with the results of the Bifenthrin study, it appears that the control rate in the Bifenthrin study (28%) is within the range reported in the open literature for this strain of mouse.

b. MTD Considerations:

Body weight gain was decreased in male mice at the highest dose tested (HDT) during week 3-18 of the study. The depression was only 4-6%; however, it was statistically significant. Body weight gain in females was significantly depressed at HDT during weeks 2 and 5 only by 4 and 3 %, respectively. Tremors occurred frequently in all mice at 500 and 600 ppm during the first 60 days of the study. The incidence of retinal atrophy was significantly elevated in both males and females at the HDT. Also, incidences of bilateral testicular germinal epithelial degeneration were elevated, but no dose response relationship was evident.

A MTD was probably not reached in this study. However, based upon tremors seen at 500 and 600 ppm in both male and female mice and a slight but statistically significant depression in body weight gain in males, a MTD was probably approached at the HDT. The results of a 28-day range finding study add support to this conclusion. In this study at 750 ppm Bifenthrin, 5/10 females died by day 6 following tremors and clonic convulsions. No male mice died at this dose.

2. Rat Oncogenicity Study:

Oncogenicity Study of FMC 54800: 2-Year (734 day) Feeding Study in Albino Rats. Mc Carty, J. D., Barbera, J., Ballester, E. J. and Geiger, L. E. Study No. A83-952. Conducted by FMC Toxicology Laboratory, Somerville, NJ. January 31, 1986. Accession Nos. 261940-261947.

[1] Prejean, J. D., Pickham, J.C., Casey, A. E., Griswold, D. P., Weisburger, E. K. and Weisburger, J. H. (1973). Spontaneous Tumors in Sprague-Dawley Rats and Swiss Mice. Cancer Res. 33:2768-2773.

[2] Buening, M. K., Levin, W., Wood, A. W., Chang, R. L., Lehr, R. E., Taylor, C. W., Yagi, H., Jerina, D.,M. and Conney, A. H. (1980). Tumorigenic Activity of Benzo(e)pyrene Derivatives on Mouse Skin and in Newborn Mice. Cancer Res. 40:203-206.

[3] Sher, S. P. (1974) Tumors in Control Mice: Literature Tabulations., Toxicology and Applied Pharmacology 30:337-359.

a. Discussion of Study:

FMC 54800 technical (88.35%; 98% cis and 2% trans isomer) was administered in the diet to groups of 50 male and 50 female Sprague-Dawley rats at levels of 0, 12, 50, 100 and 200 ppm. The duration of the study was 734 days. The incidence of various tumors possibly compound related, are outlined in the table below.

Incidence of Tumors in Sprague-Dawley Rats Fed FMC 54800

Tumor Type	Dose (ppm) 0	12	50	100	200
Males					
Fibrosarcomas	0/50(0)	1/50(2)	0/50(0)	0/50(0)	3/50(6)
Pancreas islet cell adenoma	1/47(2)	0/25(0)	0/27(0)	0/31(0)	3/50(6)
Females					
Pancreas islet cell adenoma	0/50(0)	0/23(0)	0/13(0)	0/16(0)	1/49(2)

The number in parentheses is the percentage incidence.

For neither tumor type was there a significantly elevated incidence at the HDT.

Historical control data was available on one other study conducted at this laboratory. Females were on study for 104 weeks and males for 100 weeks.

Pancreatic islet tumors	males	0/50
	females	0/50
Fibrosarcomas	males	0/51

On pancreatic islet tumors, the company also referred to the Hazleton Laboratories historical control data base on Sprague-Dawley rats. For combined sexes the mean percentage incidence of this tumor was 3.5% with a range of 2.4-5.9%. The incidence of this tumor type in the Bifenthrin study was 4% for males and females combined.

The Committee did not feel that the occurrence of either tumor type was compound related, i.e. statistical significance was not achieved

for either tumor type neither in trend analysis nor in pairwise comparison and for pancreatic islet tumors, historical control data indicates that this is not a particularly rare tumor type in this strain of rat.

b. MTD Considerations:

Doses for this study were based upon the results of a 28-day range finding study. Death accompanied by tremors occurred at 300 ppm in 6/10 males by day 12 and in 1/10 females by day 20. On this basis the HDT for the two year study was chosen at 200 ppm.

In a 90 day rat feeding study tremors and decreased body weight gain were seen at 200 ppm. The technical product used in this study contained 90% cis and 10 % trans isomer (the product used in the oncogenicity studies was 98% cis and 2% trans). Use of this study for determining an MTD for a chronic feeding study may nonetheless be appropriate because the cis isomer is more biologically active than the trans.

In the two-year feeding study tremors were seen in all animals at the HDT for the first 30 days of the study. In females, body weight gain was significantly depressed 8-10% from weeks 13 through 96. Statistically significant body weight depression was not seen in the males.

Based upon the results of the 28-day range finding study where deaths occurred within 12-20 days of chemical administration at 300 ppm and upon body weight depression (8-10%) in female rats at the HDT (200 ppm) in the 2-year feeding study, 200 ppm was an appropriate dose selection to approximate a MTD in the two year feeding study.

E. Additional Toxicology Information:

1. Metabolism:

The major route of metabolism of FMC 54800 is hydrolysis at the ester linkage. Hydroxylation of the unsubstituted phenyl ring of the intact molecule also occurs.

When rats were administered a single oral dose of FMC 54800, 83% of the radioactivity was excreted in the feces (primarily parent compound) and 8% in the urine (conjugated polar metabolites) after 7 days. Fat contained the highest concentration of radioactivity. When given daily for longer periods of time, FMC 54800 was found to bioaccumulate in fat and fatty tissues.

2. Mutagenicity:

Bifenthrin was negative in the following acceptable assays: Ames Salmonella assay, chromosome aberration assay in CHO cells, and in vivo chromosomal aberration assay in rat bone marrow cells. It was also negative in the sex-linked assay in Drosophila melanogaster, the CHO assay for point mutations at the HGPRT locus and in the in vitro transformation assay in BALB/3T3 cells. These three assays were not acceptable by present Agency

guidelines.

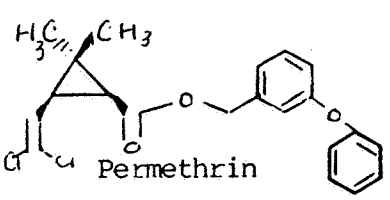
Bifenthrin was positive both with and without metabolic activation in an acceptable mouse lymphoma forward mutation assay. It was also positive for unscheduled DNA synthesis (UDS) in rat hepatocytes at 2ul/mg; however, when the assay was repeated, it was negative for UDS up to 2.5 ul/ml. Both UDS assays were acceptable.

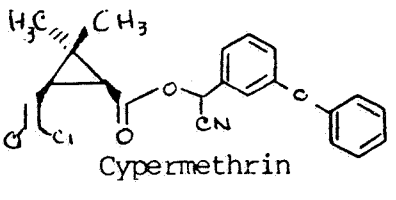
3. Reproduction and Teratology:

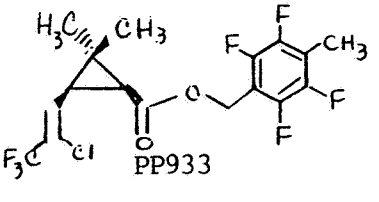
Bifenthrin was not teratogenic to either the rat or mouse but did cause fetotoxicity (hydroureter) in the rat at 2 mg/kg. In a 2-generation reproduction study, Bifenthrin administration to rats did not induce any reproductive toxicity up to 100 ppm although tremors were observed in the dams at this dosage level.

. Structure Activity Relationship:

Bifenthrin is structurally related to the following three pyrethroids:


Permethrin


Cypermethrin


PP933

Permethrin induced hepatocellular and bronchioalveolar tumors in female mice and was negative in the rat, cypermethrin induced lung tumors in female mice, and PP993 was negative in the rat for oncogenicity and has not been tested in the mouse.

In addition, the registrant does not feel that structure activity correlations should be made between permethrin and bifenthrin since data in the open literature[3] indicates that they induce the pyrethroid syndrome by different mechanisms.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Bifenthrin to be of importance in a weight of the evidence determination of oncogenic potential.

1. Administration of Bifenthrin to Swiss-Webster mice was associated with an increased incidence of leiomyosarcomas of the urinary bladder in male mice, an increased incidence of combined hepatocellular adenomas and adenocarcinomas also in male mice and an increased incidence of combined

[3] Gammon and Sander (1985) Neurotoxicology 6(2):63-86.

bronchioalveolar adenomas and adenocarcinomas in female mice.

2. Historical control data from the performing laboratory consisted of data from only one study. However, the incidence of leiomyosarcomas of the urinary bladder in this study indicated that the occurrence of these tumors is not a rare event, i.e. not less than 1%, on the other hand this tumor type is not commonly occurring, such as lung and liver tumors in mice.

3. The MTD was probably approached in the mouse study. Judging from the results of a 28-day range finding study at 750 ppm (5/10 females died by day 6), a dose not much higher than 600 ppm would not have been tolerated chronically by Swiss-Webster mice.

4. An increased incidence of pancreatic islet cell adenomas in combined male and female Sprague-Dawley rats and of fibrosarcomas in male rats was associated with Bifenthrin administration; however, statistical significance was not reached for either of these tumor types at the HDT.

5. A MTD was reached in the rat study at 200 ppm based upon the results of the 28-day range finding study where deaths occurred within 12-20 days of chemical administration at 300 ppm and upon body weight depression (8-10%) in female rats at the HDT (200 ppm) in the two-year feeding study.

6. When a single dose of Bifenthrin was administered to rats, 83% was excreted in the feces and 8% in the urine within 7 days. Bifenthrin bioaccumulates in fat and fatty tissue.

7. Bifenthrin was negative in several short term assays for mutagenicity but was positive for point mutations both with and without metabolic activation in the mouse lymphoma assay.

8. Bifenthrin was not teratogenic in either the rat or rabbit. It was fetotoxic in the rat causing hydroureter. In a two-generation reproduction study, it induced no reproductive toxicity at a dose that caused tremors in the dams.

9. Bifenthrin is structurally related to permethrin, cypermethrin and PP993. Permethrin induces hepatocellular and bronchioalveolar neoplasms in female mice and cypermethrin induces lung tumors in female mice. PP993 has not been tested for oncogenicity in the mouse but was negative in the rat.

G. Classification of Oncogenic Potential:

The Committee devoted considerable effort in the classification of Bifenthrin, based on the data before it, since it was readily apparent that Bifenthrin met criteria for both categories B_2 and C. The criteria for the B_2 category were met notably by malignancy of tumors, more than one tumor type in the same species, the uncommon occurrence of bladder leiomysarcomas and the degree of tumor response (31%) at 600 ppm in the mouse study. On the other hand the same information supported a Category C classification, most notably only one sex was affected, only one species was affected, mutagenicity assays provided only weak support for upgrading to B_2 and SAR to other pyrethroids supported a C classification. (Although the other

pyrethroids are not yet classified according to the 1986 guidelines, the previous reviews of their data sets seems to favor a C classification.) The Committee concluded that the evidence for a C classification outweighed that for a B_2 classification. This decision was further supported by the following facts: 1) The urinary bladder tumor response at 50, 200 and 500 ppm was about equal (12-16%) and was only elevated to 31% at 600 ppm, indicating no dose response; 2) Liver adenocarcinomas and adenomas/adenocarcinomas combined only showed a significant dose-trend but no significance in pairwise comparison; 3) The lung tumors showed no dose-related trend while the response at 50, 200 and 600 ppm but not at 500 ppm was statistically significant compared to controls; and 4) There was no indication that tumor formation occurred early in the study.

Although the Committee classified Bifenthrin as a Category C oncogen, they concluded unanimously that a quantitative estimation of the oncogenic potential for humans should be developed because of the uncommon nature of the urinary bladder tumors seen and of the limited but nonetheless supportive evidence derived from the incidence of both lung and liver neoplasms in the same study.

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Bifenthrin as a Class C Oncogen

---

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency's peer review classification of Bifenthrin as a Class C oncogen. The review was conducted in an open meeting held in Arlington, Virginia, on March 2, 1988. All Panel members, except Dr. Thomas W. Clarkson, were present for the review. In addition, Dr. Wendell W. Kilgore, University of California, Davis, served as an ad hoc member of the Panel.

Public notice of the meeting was published in the Federal Register on Thursday, February 18, 1988.

Oral statements were received from staff of the Environmental Protection Agency and from Dr. Martin Fletcher, FMC Corporation.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Bifenthrin

The Agency requested the Panel to focus its attention upon a scientific issue relating to the Peer Review of Bifenthrin. There follows the issue and the Panel's response to the issue:

Issue:

Does the Panel have any specific comment regarding our overall assessment of the weight-of-evidence and classification of this chemical in accordance with the Agency's Guidelines for Carcinogen Risk Assessment.

Panel Response:

The Panel agrees that bifenthrin is best classified as a category C oncogen. This opinion is based on the significant occurrence only at the high dose of leiomyosarcomas in urinary bladders of male mice. However, the Panel does not believe that quantitative risk assessment is warranted. This opinion is based upon the lack of any dose response data in any animal model and the inappropriateness in applying mathematical models to data that do not show a dose response.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 3-9-88

6/9/88

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FILE COPY

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 9 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Second Peer Review of Bifenthrin - Reevaluation Following the March 2, 1988 Science Advisory Panel Review

From: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 5/4/88
Section Head, Section VI
Toxicology Branch/HED (TS-769C)

To: George LaRocca
Product Manager #15
Registration Division (TS-767C)

The Peer Review Committee met on March 30, 1988 to examine the issues raised by the Science Advisory Panel (SAP) with respect to the classification of the carcinogenicity of Bifenthrin.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated).

Reto Engler _____

William Burnam _____

Esther Rinde _____

Richard Levy _____

Marion Copley _____

Lynnard Slaughter _____

Kerry Dearfield _____

2. Reviewers: (non-panel members responsible for data presentation signatures indicate technical accuracy of panel report).

Byron T. Backus (Reviewer) _____

Marcia van Gemert (Section Head) _____

3. Peer Review Members in Absentia: (Committee members who were inable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

48

Theodore M. Farber	Theodore M. Farber
Anne Barton	
Judith W. Hauswirth	Judith W. Hauswirth
John A. Quest	John A. Quest
Robert Beliles	Robert Beliles
Diane Beal	Diane L. Beal
Richard Hill	

B. Material Reviewed:

The SAP response memorandum from the March 2, 1988 meeting was reviewed by the Committee.

C. Considerations:

The Panel agreed with the Committee's overall assessment of the weight of the evidence on Bifenthrin, classifying it as a category C oncogen. However, they did not agree that a quantification of risk should be performed, since there was a "lack of any dose response data in any animal model and [because of] the inappropriateness in applying mathematical models to data that do not show a dose response".

Issues:

Quantification of Risk:

The Committee originally felt unanimously (Peer Review memorandum dated June 2, 1987) that a quantitative estimation of the oncogenic should be performed because of the uncommon nature of the urinary bladder tumors seen in the Swiss-Webster mice and because of the limited but supportive evidence derived from the incidence of both lung and liver neoplasms seen in the same study.

Arguments against a quantification of risk discussed at the March 30, 1988 meeting were that the bladder tumors were seen only in male mice, only at the highest dose tested and were not supported by any SAR information.

The Committee was divided on whether a quantification of risk should be performed but favored quantification because of the uncommon nature of the tumor type.